Factors Influencing Age and Strain-Related Susceptibility to 3-Methylcholanthrene Carcinogenicity

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Fetal mice are more sensitive to chemical carcinogens than are adults. Further, some strains of mice are more susceptible to chemical carcinogens than others. We have been conducting studies to understand the interactions between age and genetic background underlying these susceptibilities. Previous studies from our laboratory demonstrated differences in the mutational spectrum induced in the Ki-*ras* gene from lung tumors isolated from [D2 x B6D2F1]F2 mice and Balb/c mice treated *in utero* with 3-methylcholanthrene (MC). We hypothesized that differences in susceptibility to MC might be due to age- and strain-related differences in metabolism and formation of DNA damage. We thus determined whether differences in metabolism, adduct formation, glutathione-S-transferase activity, or adduct repair influence strain-specific responses to transplacental MC exposure in C57BL/6, Balb/c, and reciprocal F1 crosses between these two strains of mice. The overall kinetics and patterns of induction of *Cyp1a1* and *Cyp1b1* were very similar across the four strains of mice. The only significant strain-specific effect appeared to be the relatively poor induction of *Cyp1b1* in parental C57BL/6 mice, especially in fetal lung tissue. We also measured the levels of MC adducts and their disappearance from lung tissue on gestation days 18 and 19 and postnatal days 1, 4, 11, and 18. No significant differences were seen between the different strains of mice.

These results indicate that differences in Phase I metabolism of MC and formation of MC-DNA adducts are unlikely to account for the marked differences observed in the tumorigenicity and Ki-*ras* mutational spectra seen in previous studies. Although strain-specific differences in the expression of the *GST* isozymes that were independent of MC treatment were observed, they could not account for the differences previously observed in either the Ki-*ras* mutational spectrum or lung tumor incidence in the different strains of mice. Similar results were obtained when the maternal metabolism of MC was assayed in liver microsomal preparations. The results are consistent with previous studies showing low levels and poor inducibility of Phase II enzymes during gestation and demonstrate for the first time that all four of the major *GST* isozymes are expressed in fetal tissues. While the high inducibility of activating enzymes, such as *Cyp1a1*, and low, uninducible levels of Phase II conjugating enzymes probably account for the high susceptibility of the fetus to transplacentally induced tumor formation, the results also suggest that genetic factors other than metabolism may account for the strain-specific differences in susceptibility to carcinogen-mediated lung tumor induction following *in utero* exposure to chemical carcinogens.

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